C. REMARKS

Claims 30, 37, 44, 51, and 58 have been amended in order to place such claims in better form. It is to be understood, however, that the amendment of such claims is not to be construed as an admission by Applicants or Applicants' attorneys that Claims 30, 37, 44, 51, and 58, prior to the amendment thereof, were unpatentable.

Claims 28-30, 34-37, 41-44, 48-51, 55-58, and 62-77 stand rejected under 35 U.S.C. 102(e) as being anticipated by Abatangelo, et al.

Claims 28, 31-33, 35, 38-40, 42, 45-47, 49, 52-54, 56, and 59-61 stand rejected stand rejected under 35 U.S.C. 102(b) as being anticipated by Goldberg, et al.

These rejections are respectfully traversed.

The present invention is directed to regenerating meniscal tissue in a joint and thereby to reducing or preventing changes in the joint resulting from meniscal damage, including reducing subchondral bone sclerosis in a joint, preventing or reducing the formation of osteophytes in a joint, and protecting cartilage in a joint of an animal, by injecting into the joint a liquid suspension consisting essentially of mesenchymal stem cells and an acceptable pharmaceutical carrier. The mesenchymal stem cells differentiate into and/or stimulate production of meniscal tissue.

The cited prior art is directed to the delivery of mesenchymal stem cells as part of a solid cell-matrix construct to a joint, or to the use of mesenchymal stem cells to treat osteoarthritis.

Applicants submitted previously evidence, i.e., the Walsh paper, which has been made of record, which emphasizes the importance of providing mesenchymal stem cells in a solid implant having sufficient tensile strength. The prior art teaches away from Applicants' invention as claimed, wherein a liquid suspension, as opposed to a solid implant, containing mesenchymal stem cells is injected into a joint. Also, such injection of a liquid suspension of mesenchymal

stem cells, as claimed by Applicants, prevents osteoarthritis, as opposed to the treatment of osteoarthritis after osteoarthritis has developed.

The Examiner bases his rejection under 35 U.S.C. 102 (e) upon two passages in Abatangelo: (i) Column 8, lines 20-37; and (ii) Example 7.

Column 8, lines 20-37 states that the cell biomatrix may be any of a variety of forms, such as a sponge, a dimensionally stable matrix, a matrix having a moldable putty-like consistency, a pliable gel or slurry, a powder, or an injectable fluid.

Example 7 discloses the use of the cell matrix and mesenchymal stem cells in a meniscus repair study. Example 7 states that composites were prepared as described in Example 6. Example 6 describes the composites as suspensions of mesenchymal stem cells that were loaded onto solid hyaluronic acid based carriers. Example 7 states that the composites were sutured to the lateral meniscus, the coronal meniscus, the synovial lining, and the posterior half of the meniscus. Thus, Example 7 teaches the repair of meniscus with an implant including bone marrow derived cells that were absorbed or loaded onto a solid hyaluronic acid based carrier, and the implant was sutured to a damaged meniscus.

Although Column 8, lines 20-37 state that the matrix may be in any of a variety of solid forms or in the form of an injectable liquid, there is nothing in Abatangelo which directs those skilled in the art clearly and unequivocally to select and administer an injectable suspension of mesenchymal stem cells in a hyaluronan based carrier when repairing meniscal tissue, and there is no indication in Abatangelo that Abatangelo ever selected an injectable suspension of mesenchymal stem cells in a hyaluronan based carrier when repairing meniscal tissue. In fact, when Abatangelo undertook an experiment to repair damaged meniscal tissue, Abatangelo elected to use a solid hyaluronic acid based implant containing bone marrow derived cells. Thus, Abatangelo provides no direction to one skilled in the art to select a liquid hyaluronan based

carrier for mesenchymal stem cells when employing such mesenchymal stem cells in repairing damaged meniscal tissue. Therefore, Abatangelo does not anticipate applicants' claimed invention under 35 U.S.C. 102 (e). (See In Re Arkley, 172 U.S.P.Q. 524 (C.C.P.A. 1972), at 526.)

Furthermore, in Example 7, at Column 14, lines 52-54, it is stated that "The knee joint was carefully dissected and the meniscus harvested and processed for histological analysis." There are, however, no results provided by Abatangelo of such analysis. Thus, Abatangelo provides no evidence that the implantation of the esterified hyaluronic acid carrier containing mesenchymal stem cells resulted in meniscal repair. Even if there were results that did show that the implant of Abatangelo was implanted successfully, the only teaching contained in Abatangelo regarding the regeneration and/or repair of meniscal tissue is to employ a solid implant containing mesenchymal stem cells. In fact, all of Albatangelo's examples, not just the example directed to the repair of meniscal tissue, are directed to the use of solid implants. Abatangelo, which is directed solely to the implantation of a solid carrier containing mesenchymal stem cells into a joint in an attempt to repair meniscal tissue, does not even remotely suggest to one of ordinary skill in the art that one can repair meniscal tissue by injecting into a joint a liquid suspension consisting essentially of mesenchymal stem cells. Furthermore, Abatangelo, when combined with Walsh, would teach one of ordinary skill in the art to regenerate and/or repair meniscal tissue by using a solid implant containing mesenchymal stem cells, provided that the solid implant has sufficient tensile strength to be anchored to the joint, and that the implant does not elicit an inflammatory response. Thus, Abatangelo and Walsh teach away from repairing and/or regenerating meniscal tissue by injecting into a joint a liquid suspension of mesenchymal stem cells, as claimed by Applicants. Such teaching away clearly is indicative of non-anticipation and non-obviousness. (See W.L. Gore & Associates,

Inc. v. Garlock, Inc., 220 U.S.P.Q. 303 (C.A.F.C. 1983), at 312; United States v. Adams, 383 U.S. 39 (1966)).

Thus, Abatangelo does not anticipate Applicants' methods as claimed, nor does Abatangelo render Applicants' methods as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102 (e) be reconsidered and withdrawn.

Goldberg is directed to the administration of mesenchymal stem cells in the treatment of osteoarthritis. Goldberg discloses the use of animal models to induce osteoarthritis, followed by the administration of mesenchymal stem cells in order to repair articular cartilage damage resulting from osteoarthritis. In one model, i.e., a rabbit model, a partial meniscectomy is performed. This induces osteoarthritis in the rabbit, as well as the cartilage degeneration resulting therefrom.

Goldberg desires to repair articular cartilage damage caused by osteoarthritis by administering mesenchymal stem cells. There is no disclosure or suggestion in Goldberg to repair meniscal tissue as claimed by Applicants.

The Examiner is taking the position that, if one follows the teachings of Goldberg, that one inherently will repair meniscal tissue and thus Goldberg anticipates the claimed invention. In making such a rejection, however, the Examiner has overlooked that:

> "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient". (In Re Robertson, 169 F.3d 743 (Fed. Cir. 1999), at 745, 49 U.S.P.Q. 2d 1949, at 1950-1951, citing Continental Can Co. v. Monsanto Co., 948 F.2d 1264 (Fed. Cir. 1991), at 1269, 20 U.S.P.Q. 2d 1746, at 1749, and In Re Oelrich, 666 F.2d 578 (Ct. Cust. Pat. App. 1981), at 581, 212 U.S.P.Q. 323, at 326). (emphasis added).

As will be explained in further detail hereinbelow, all that Goldberg discloses is that an injectable suspension of mesenchymal stem cells may be used to regenerate damaged articular cartilage as a result of osteoarthritis. There is nothing in Goldberg which would lead one skilled

in the art to believe that by following the teachings of Goldberg, one also can repair meniscal tissue. Assuming solely for the sake of argument that, by following the teachings of Goldberg, one may repair damaged meniscal tissue, such a result is only a mere possibility in that Goldberg is directed to the regeneration of articular cartilage, and there is nothing in Goldberg which states that using an injectable suspension of mesenchymal stem cells to regenerate articular cartilage defects also will repair meniscal tissue. Therefore, there is no basis in Goldberg for asserting that following the teachings of Goldberg also result inherently in the repair of meniscal tissue which, as stated hereinbelow, has properties different from that of articular cartilage.

Furthermore, Applicants assert that:

> "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence."
> (Continental Can, supra, 948 F.2d 1264, at 1268, 20 U.S.P.Q. 2d 1746, at 1749).

Goldberg is silent with respect to whether, if one uses the injectable suspension of mesenchymal stem cells disclosed in Goldberg to repair articular cartilage defects, one also inherently will repair meniscal tissue. Because Goldberg is silent with respect to whether, in regenerating articular cartilage, one also repairs meniscal tissue, it is incumbent upon the Examiner to present extrinsic evidence which shows that the articular cartilage repair treatments disclosed by Goldberg also necessarily will result in the repair of meniscal tissue. The Examiner has failed to provide any such extrinsic evidence, and therefore any assertion by the Examiner that meniscal tissue repair inherently will result by following the teachings of Goldberg is based on mere possibilities, and therefore is insufficient to support the anticipation rejection based upon Goldberg.

More particularly, Goldberg's rabbit meniscectomy model is performed in order to induce osteoarthritis and the articular cartilage damage caused by osteoarthritis. The mesenchymal stem cells then are administered in order to determine whether the mesenchymal

stem cells will differentiate into cartilage, and thus repair the articular cartilage damage caused by the induced osteoarthritis. Goldberg does not administer the mesenchymal stem cells in order to repair or regenerate meniscal tissue.

By repairing meniscal tissue, Applicants prevent osteoarthritis from occurring. In contrast, Goldberg discloses the administration of mesenchymal stem cells after osteoarthritis has developed, and there is nothing in Goldberg that even remotely suggests to one of ordinary skill in the art that such administration of mesenchymal stem cells after the onset of osteoarthritis results in the repair of meniscal tissue. Goldberg is directed solely to the treatment of osteoarthritis and the repair of articular cartilage damaged as a result of osteoarthritis. Nothing in Goldberg's disclosure would lead one of ordinary skill in the art to expect reasonably that mesenchymal stem cells may be administered to a joint in order to repair meniscal tissue and thus prevent osteoarthritis.

Furthermore, Goldberg's sole objective of regenerating articular cartilage that has been damaged as a result of osteoarthritis is mentioned throughout the Goldberg application, as exemplified by the following passages:

> "Once the condition [i.e., osteoarthritis] has progressed to substantial articular cartilage damage, none of the currently available approaches are adequate."

(Page 3, lines 17-19)

> "The most promising approach to articular cartilage repair appears to be the use of autologous mesenchymal stem cells, which are osteochondral precursors."

(Page 5, lines 18-20)

> "A characteristic indicator of chondral defect is a visibly altered gait or use of the joint to accommodate the discomfort or stiffness resulting from tissue damage, and the objective of treatment is to regenerate full thickness articular cartilage at the site of the defects to thereby prevent the joint destabilization and rapid joint

destruction which are common sequelae of advanced osteoarthritis."

"Patients ranging in age from 30-50 years with one or more well-defined articular cartilage lesions (as determined by imaging modalities or diagnostic arthroscopy) are ideal candidates for treatment in accordance with the invention."

(Page 6, lines 15-27)

"The implants of the invention are indicated for use in regenerating articular cartilage which has been lost through degenerative osteoarthritis."

(Page 11, lines 4-6)

"Implants containing autologous human mesenchymal stem cells are chondrogenic and, as such, regenerate hyaline cartilage directly at the graft site where they are able to differentiate into cartilage-forming chondrocytes."

(Page 11, lines 10-13)

Regulation of Chondrogenesis

"This aspect focuses on the identification of molecules regulating mesenchymal stem cells during chondrogenic differentiation, including factors controlling the development of articular hyaline cartilage. To regenerate hyaline cartilage in osteoarthritis patients under a variety of clinical scenarios, it is important to develop a better understanding of the molecules that control the chondrogenic lineage progression of human mesenchymal stem cells."

(Page 17, line 28 – Page 18, line 3)

".... 2) once committed, the mesenchymal stem cell-derived progeny cells are capable of progressing toward articular chondrocytes."

(Page 18, lines 13-15)

"The implant, device and/or composition of the invention utilizes autologous mesenchymal stem cells in a gel, liquid, or molded configuration to regenerate the articular, hyaline cartilage via the developmental course seen during embryonic differentiation."

(Page 30, line 33 – Page 31, line 2)

> "The mesenchymal stem cells in the liquid suspension home directly towards the sites of lesions on the articular surface."

(Page 31, lines 30-32)

> "The ultimate goal of the product development program is to regenerate articular cartilage destroyed by osteoarthritis."

(Page 34, lines 12-14)

Applicants' claimed invention, in contrast, is directed to the repair and regeneration of meniscal tissue. Meniscal tissue is not articular cartilage. Articular cartilage is hyaline cartilage, while meniscal tissue is fibrocartilage. (See Buckwalter, et al., Orthopaedic Basic Science, 2nd Edition, American Academy of Orthopaedic Surgeons, Chapter 17, page 444, column 2, lines 17 and 18, page 445, column 2, line 15 and page 446, column 1, line 6, Table 1, page 445, Figure 3, page 446, and Chapter 20, page 532, column 1, lines 2 and 3. A copy of Chapters 17 and 20 of Buckwalter accompanies this Amendment.)

The Examiner bases his rejection upon two passages in Goldberg i.e., Page 4, line 33 to Page 5, line 9 and Page 6, lines 1-9.

Page 4, line 33 to Page 5, line 9 reads as follows:

> For repair of cartilage damaged as part of the degenerative effects of osteoarthritis; the present inventors have found that the human mesenchymal stem cell approach makes it possible to: (1) regenerate both shallow cartilage chondral defects and full thickness cartilage defects (osteochondral lesions); (2) broaden the suitable clinical population to routinely include middle-aged patients; (3) eliminate the use of autologous tissue grafts (mature cartilage and the periosteal covering) to repair an articular cartilage injury; (4) regenerate other types of cartilage such as patellar and spinal disk cartilage; (5) regenerate articular joint cartilage in older patients with osteoarthritis; and (6) form new cartilage and subchondral bone which fully integrate into the adjacent normal tissue.

None of the above-mentioned applications, however, is directed to the repair of meniscal tissue.

Page 6, lines 1-9 read as follows:

> Several formulations of autologous, culture-expanded mesenchymal stem cells that serve as the basis of therapies for osteoarthritis are contemplated depending on the stage, joint location and severity of the disease. They are (1) a gel formuation that can be applied to osteochondral defects during arthroscopy; (2) an injectable cell suspension for delivery directly to the synovial space; and (3) a molded mesenchymal stem cell-biomatrix product to re-surface joint surfaces in advanced cases.

This passage, when read in context with the two paragraphs following such passage such two paragraphs including Page 6, lines 15-27 cited hereinabove, indicates clearly to one skilled in the art that the injectable cell suspension would be used to repair articular cartilage defects, as opposed to meniscal tissue as claimed by Applicants.

Therefore, the two passages of Goldberg provide no basis for a rejection under 35 U.S.C 102(b).

In addition, as stated previously in Applicants' Amendment filed January 14, 2003, meniscus and articular cartilage have different compositions, structures, and mechanical functions. The major macromolecule in the meniscus is Type I collagen, which has two $\alpha 1$ chains and one $\alpha 2$ chain. (See Adams, et al., Knee Meniscus: Basic and Clinical Foundations, Chapter 2, pages 15-28, Raven Press, Ltd., New York, (1992), a copy of which was submitted with Applicants' Amendment filed January 14, 2003), while the major component of articular cartilage is Type II collagen, which has three $\alpha 1$ chains. (See also, Naumann, et al., J. Histochem. and Cytochem., Vol. 50, No. 8, pages 1049-1058 (2002), at Table 2, page 1053. A copy of Naumann accompanied the Amendment of January 14, 2003.) In addition, although some Type X collagen is found in articular cartilage, no Type X cartilage has been found in meniscus. Furthermore, meniscus contains significantly less glycosaminoglycans (GAG) than hyaline cartilage. (See Naumann, at page 1053, column 2, lines 17-20 and 32-35, and Table 2.)

The collagen content of articular cartilage is about 60% of the dry tissue weight (Mankin, et al., Osteoarthritis, Diagnosis and Medical/Surgical Management, Chapter 5, Moskowitz, et al., Eds., Philadelphia, W.B. Saunders Company (1992), pages 109-154, at page 111, a copy of which was submitted with Applicants' Amendment filed January 14, 2003), while meniscus has a collagen content up to 75% of its dry tissue weight. (See Adams, et al., page 17, column 2, line 27.) The proteoglycan content of the meniscus has been reported to be from about one-twentieth to about one-eighth of that in articular cartilage. (See Buckwalter, et al., at page 534, column 1, lines 25-27 and Adams, et al., page 22, column 2, lines 9-11.)

In addition, articular cartilage is divided into superficial, intermediate, and deep zones; and the collagen fiber orientations and proteoglycan contents vary in each zone. In the meniscus, the collagen fibers predominantly are in a circumferential arrangement, and they act as reinforcement for the meniscus to resist tensile stresses. (See Adams, et al., pages 19 and 20 and Buckwalter, et al., page 533, column 2, line 35 to page 534, column 1, line 1.)

Also, the stiffness of the meniscus along the collagen fibers (i.e., in the circumferential direction) is one to two orders of magnitude higher than that of articular cartilage. (See Setton, et al., Clinical Orthopaedics and Related Research, number 367S, pgs. S254-S272, Lippincott, Williams & Wilkins, 1999, a copy of which was submitted with Applicants' Amendment filed January 14, 2003). This high stiffness along the collagen fibers enables the meniscus to resist large circumferential stresses that arise when it is loaded. The resistance to fluid flow (which is proportional to the inverse of the hydraulic permeability) of the meniscus is about 6 to 10 times that of articular cartilage, so that the meniscus resists fluid exudation to a greater extent than cartilage.(See Setton, et al., pg. S258, column 2 and pg. S259, column 1, and Buckwalter, et al., pg. 535, column 2, lines 6-9). The lower permeability of the meniscus allows the meniscus to remain pressurized for longer time periods after loading, so the meniscus acts as a fluid-filled

cushion. In addition, meniscus has approximately half the elastic modulus of articular cartilage. (See Buckwalter, et al., page 535, column 2, lines 6-9.) Because meniscus and articular cartilage have different compositions, structures, and mechanical functions, Goldberg, which discloses the use of mesenchymal stem cells to regenerate damaged articular cartilage as a result of osteoarthritis, provides no basis for one of ordinary skill in the art to believe that the regeneration of articular cartilage also inherently will result in the repair of meniscal tissue. Therefore, Goldberg does not anticipate the claimed invention, and provides no basis for one of ordinary skill in the art to provide Applicants' claimed methods of regenerating meniscal tissue and repairing meniscal damage in a joint.

Because Goldberg does not disclose or even remotely suggest to one of ordinary skill in the art the repair of meniscal tissue by injecting into a joint a liquid suspension including mesenchymal stem cells, Goldberg does not anticipate Applicants' invention as claimed, nor does Goldberg render Applicants' invention as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102 (b) be reconsidered and withdrawn.

Furthermore, the combination of Abatangelo and Goldberg does not render Applicants' method as claimed obvious to one of ordinary skill in the art. While injection of mesenchymal stem cells is taught by Goldberg for repair of articular cartilage in osteoarthritis, Abatangelo clearly teaches the use of solid supports for cell delivery and teaches away from the injection of a liquid suspension of mesenchymal stem cells for repair of meniscal tissue, thereby rendering the injection of a liquid suspension of mesenchymal stem cells non-obvious for meniscal tissue repair.

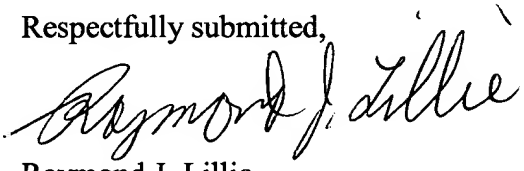
For the above reasons and others, Abatangelo and Goldberg also do not render Applicants' method as claimed obvious to one of ordinary skill in the art.

With respect to the rejection of Claims 30, 37, 44, 51, and 58 under 35 U.S.C. 112, first paragraph, such claims have been amended in order to define the hyaluronan or salt thereof as sodium hyaluronan. Support for such claims as amended is found in the specification at Pages 7, 8, 23, and 25.

For the above reasons and others, Claims 30, 37, 44, 51, and 58 are patentable over 35 U.S.C. 112, first paragraph, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,



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